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Adherence and persistence to hyperlipidemia medications in patients with atherosclerotic cardiovascular disease and those with diabetes mellitus based on administrative claims data in Japan

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HIGHLIGHTS

- This longitudinal cohort study analyzed hyperlipidemia (HL) therapy claims data.
- Patients with type 2 diabetes mellitus or cardiovascular disease were included.
- Adherence was ≥80% across most drug classes in both cohorts.
- 12-month persistence rates were low and variable, and warrant further study.

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ABSTRACT

Background and aims: Real-world data on treatment patterns in Japanese hyperlipidemia patients with diabetes mellitus (DM) or prior atherosclerotic cardiovascular diseases (ASCVD) are lacking.
Methods: This is a retrospective, longitudinal cohort analysis of administrative claims data (Japan Medical Data Center [JMDC] and Medical Data Vision [MDV] databases) for patients prescribed a new hyperlipidemia medication between 2014 and 2015. Patients were followed for ≥12 months. Outcomes included prescribing patterns, persistence (discontinuations), and adherence (proportion of days covered).
Results: Data were analyzed for 11,718 and 27,746 DM, and 4101 and 14,356 ASCVD patients from the JMDC and MDV databases, respectively. Among previously-untreated patients, index prescriptions were primarily for moderate statins in the DM (JMDC: 74.7%, MDV: 77.5%) and ASCVD (JMDC: 75.4%, MDV: 78.5%) sub-cohorts. Combinations were rarely prescribed (≤2.5%). Previously-treated patients were most frequently prescribed combinations in the DM (JMDC: 46.7%, MDV: 53.6%) and ASCVD (JMDC: 49.3%, MDV: 53.3%) sub-cohorts. Intensive statins were rarely used by previously-untreated (≤1%) or previously-treated (≤8%) patients in either sub-cohort. Approximately half of previously-untreated patients discontinued hyperlipidemia therapy within 12 months. Adherence was ≥80% across most drug classes.
Conclusions: Many Japanese hyperlipidemia patients with DM or ASCVD are prescribed single-agent lipid-lowering therapy. Use of intensive therapy is lower than expected, and is suggestive of under-treatment. The low persistence rates are concerning, and warrant further study.

1. Introduction

Hyperlipidemia, defined as abnormally increased levels of blood lipids or lipoproteins (most commonly low-density lipoprotein (LDL)-cholesterol [LDL-C]), is a well-established risk factor for atherosclerotic cardiovascular disease (ASCVD) and all-cause mortality [1–3]. The probability of major cardiovascular events or death is increased further in patients with additional risk factors, such as type 2 diabetes mellitus (DM), or a history of cardiovascular disease (CVD, e.g., peripheral or coronary artery disease [PAD or CAD]) or cerebrovascular disease (e.g.,

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stroke) [2,4–7].

The 2012 and 2017 guidelines from the Japan Atherosclerosis Society (JAS) recommend lipid-lowering therapy (LLT) for the primary and secondary prevention of ASCVD in patients with hyperlipidemia, if lifestyle modifications alone have failed to reduce lipid levels to below target values [2,8]. LLTs recommended by the JAS include statins, anion exchange resins, the small intestine cholesterol transporter inhibitor (SICTI) ezetimibe, fibrates, nicotinic acid derivatives, probucol, and polyunsaturated fatty acids (PUFA), such as ethyl icosapentate and omega-3-acid ethyl esters [8,9]. Because additional risk factors substantially increase the likelihood of morbidity and mortality, strict lipid management targets are recommended for patients with comorbidities including DM and PAD, with an LDL-C target 20 mg/dL lower than that recommended for patients without these comorbidities (< 120 *vs.* 140 mg/dL, respectively) [2,8,9]. For patients with a history of CAD, the LDL-C target is even lower (< 100 mg/dL) [2,8,9]. Lipid management targets can be achieved through use of single LLTs or combination therapies. Combination therapy with several classes of drugs is recommended by the JAS for patients with pre-existing CAD, or if lipid levels are not controlled by monotherapy [2,8,9].

LLT can only be optimally effective if patients adhere to their prescribed treatment regimen and continue (persist) to take their treatment over its intended course [10].

These issues are particularly relevant in patients with hyperlipidemia, where factors such as the lack of symptoms and poor awareness of the risks associated with the condition can result in poor adherence and persistence with prescribed treatment, and consequently low rates of attainment of lipid management targets [7,11–17].

The efficacy and tolerability of LLT is well documented in clinical trials, including studies of Japanese patients [2,7], but data on 'real-world' treatment patterns, and persistence and adherence between different hyperlipidemia drug classes, are lacking in Japan. To address this, a recent longitudinal cohort study, based on administrative claims data from two large databases in Japan (the Japan Medical Data Center [JMDC] and Medical Data Vision [MDV] databases) reported differences in the prescription patterns of hyperlipidemia drug classes according to the stage of treatment [18]. Previously untreated (UT) patients were most likely to be prescribed single-agent moderate statins as first-line therapy, while previously treated (PT) patients were most likely to be prescribed combination regimens. While adherence rates were generally high (≥80% in most patient subgroups), persistence rates were low, with more than half of UT patients discontinuing treatment during the 12-month observation period. Following on from this 'real-world' investigation, the JMDC and MDV databases were interrogated further in a sub-study to explore differences in the prescribing patterns of, persistence with, and adherence to LLT at a class level specifically among patients with additional risk factors, i.e., patients with DM and ASCVD patients with a history of PAD, coronary heart disease (CHD), or stroke.

2. Materials and methods

2.1. Study

This study was a retrospective, longitudinal, observational, cohort analysis of medical insurance claims data for patients in clinical practice in Japan who were prescribed a new medication for hyperlipidemia between January 1, 2014 and December 31, 2015. Results for the entire patient cohort have been reported previously [18]. Anonymized patient-level data were extracted from the JMDC and MDV administrative claims databases (Supplementary Methods). In accordance with the Ethical Guidelines for Epidemiological Research published by the Japanese Ministry of Health, Labor, and Welfare, ethics approval and informed consent were not required. The study complied with the International Society for Pharmacoepidemiology Guidelines for Good Pharmacoepidemiology Practices. All authors had full access to all data, and take responsibility for its integrity and the data analysis.

2.2. Study population

Patients were included if they were aged ≥18 years with ≥1 diagnosis of hyperlipidemia (ICD-10 code: E78) and ≥1 prescription within a target hyperlipidemia drug class (Supplementary Methods) issued between January 1, 2014 and December 31, 2015 (selection period). Only patients issued with a new prescription for hyperlipidemia during the selection period were included. Patients were also required to have ≥12 months of continuous enrollment in the database before ('pre-index period') and after ('post-index period') the index date without prescription of the index drug class within the pre-index period. The index date was defined as the date of first prescription for a target hyperlipidemia drug class initiated during the selection period; the index drug class was defined as the first therapy within a target drug class prescribed during the selection period. In situations where follow-up/enrollment information was missing from the MDV database, patients had to have ≥1 medical claim in each quarter of the pre-index period to allow longitudinal analysis.

This analysis reports hyperlipidemia drug treatment patterns, persistence, and adherence data for two sub-cohorts of patients with DM and ASCVD, respectively. Patients in the DM sub-cohort had to have a diagnosis of type 2 DM, an observed Hb1Ac level of > 6.5%, or ≥1 prescription for a DM medication within the 3 months before the index date. Patients in the ASCVD sub-cohort had to have ≥1 of the following diagnoses within the pre-index period: stroke (ICD10 code: I61, I63, or I64), PAD (ICD10 code: I70), or CHD (ICD10 code: I21, I22, or I24).

2.3. Study objectives and outcomes

The objectives of this sub-study were to determine and compare treatment persistence and adherence to therapies within hyperlipidemia drug classes in patients with hyperlipidemia and DM or ASCVD; these were pre-specified secondary objectives of the main study [18]. Outcomes were determined for the two sub-cohorts, and for UT and PT patient sub-groups within each sub-cohort. UT patients were defined as those without a prescription for any therapy within a hyperlipidemia drug class of interest during the pre-index period. PT patients were defined as those with a prescription for ≥1 non-index hyperlipidemia drug class during the pre-index period and for whom the prescription for this drug class was changed.

Treatment persistence was defined as the time from the index date until discontinuation of ≥1 of the index hyperlipidemia drug classes. A drug class was considered to be discontinued when there was no prescription renewal for the given drug class during a period greater than the 'grace period', defined as 1.5 times the median prescription duration for agents within the drug class under consideration. Persistence measures included time to discontinuation and hyperlipidemia drug class persistence rate at 12 months from the index date. For patients prescribed ≥2 hyperlipidemia drug classes concomitantly, the date of discontinuation was the date of the last prescription before the first discontinuation of any drug in the combination, plus the days of supply of that prescription.

Adherence to a therapy within a hyperlipidemia drug class of interest was defined as the proportion of days covered (PDC) or the period in which patients had the treatment in their possession. For each hyperlipidemia drug class, adherence was calculated as:

$$PDC = \frac{\Sigma \text{ days of supply over the dispensing period (index date to discontinuation)}}{\Sigma \text{ days in dispensing period (index date to discontinuation)}}$$

Patients were deemed to be adherent if they had PDC ≥80%. Analyses of adherence were performed on patients with ≥2 prescriptions of the index hyperlipidemia drug class during the 12-month post-index follow-up period.

2.4. Statistical analyses

Patient demographics, clinical characteristics, adherence, and 12-month continuation rate were analyzed using descriptive statistics. Time to drug discontinuation was determined using Kaplan–Meier methods. The first discontinuation of the index hyperlipidemia drug was the event and patients were censored if they reached the end of follow-up without discontinuation. All analyses were undertaken by Creativ-Ceutical using SAS version 9.3 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patients

Overall, 185,497 patients in the JMDC database and 704,577 in the MDV database had ≥1 prescription for an agent within a hyperlipidemia drug class of interest between January 1, 2014 and December 31, 2015. For the DM sub-cohort, 11,718 patients (6.3%) in the JMDC database (UT: 8883; PT: 2835) and 27,746 (3.9%) in the MDV database (UT: 18,422; PT: 9324) met the eligibility criteria and were included in the analyses (Supplementary Fig. 1). For the ASCVD sub-cohort, 4101 patients (2.2%) in the JMDC database (UT: 2948; PT: 1153) and 14,356 (2.0%) in the MDV database (UT: 9201; PT: 5155) were included in the analyses (Supplementary Fig. 2).

The demographics and baseline characteristics of patients are shown in Table 1 for both DM and ASCVD sub-cohorts. Mean duration of follow-up was 717 (JMDC) or 792 (MDV) days in the DM sub-cohort, and 711 (JMDC) or 791 (MDV) days in the ASCVD sub-cohort. Across both sub-cohorts, compared with patients in the MDV database, patients in the JMDC database were younger, had a higher proportion of men, were prescribed fewer concomitant drugs at the index date, had a lower proportion of PT patients, and had fewer comorbidities. Across both sub-cohorts and databases, UT patients were prescribed fewer concomitant drugs at the index date than PT patients.

In the DM sub-cohort, almost all patients had a diagnosis of type 2 DM (JMDC: 95.6%; MDV: 98.6%) (Table 1). Within this sub-cohort, a lower proportion of JMDC versus MDV patients had concomitant hypertension (53.4% *vs*. 73.2%). Rates of all other recorded hyperlipidemia-related comorbidities were also numerically lower among JMDC versus MDV patients. In the DM sub-cohort, UT patients were less likely to have hypertension than PT patients (JMDC: 49.2% *vs*. 66.5%; MDV: 70.4% *vs*. 78.8%).

In the ASCVD sub-cohort, a lower proportion of JMDC versus MDV patients had a diagnosis of stroke (29.0% *vs*. 46.8%; one of the diagnoses used to define ASCVD), type 2 DM (38.6% *vs*. 59.5%), and hypertension (61.6% *vs*. 81.0%) (Table 1). Incidences of the other high risk-defining conditions, PAD (45.8% *vs*. 46.1%) and CHD (14.0% *vs*. 14.3%), were similar across the two databases. In this sub-cohort, UT patients were less likely to have comorbid type 2 DM (JMDC: 34.2% *vs*. 50.0%; MDV: 55.1% *vs*. 67.3%), hypertension (JMDC: 58.2% *vs*. 70.5%; MDV: 79.2% *vs*. 84.2%), or PAD (JMDC: 43.5% *vs*. 51.7%; MDV: 41.1% *vs*. 55.1%) than PT patients. UT patients were more likely to have comorbid stroke (JMDC: 31.0% *vs*. 23.9%; MDV: 49.9% *vs*. 41.3%).

3.2. Treatments

Regardless of the database population (JMDC or MDV) or sub-cohort (DM or ASCVD), distributions of the index hyperlipidemia drug classes of interest among UT and PT patients were generally comparable (Figs. 1 and 2).

Among UT patients in the DM sub-cohort, the most common hyperlipidemia drug class prescribed as first-line treatment was a moderate statin (JMDC: 74.7%, MDV: 77.5%), followed by a fibrate (JMDC: 12.6%, MDV: 7.1%), and a PUFA (JMDC: 6.0%, MDV: 6.7%) (Fig. 1A). Combination therapy was rarely used as the index prescription in UT patients (JMDC: 2.1%; MDV: 1.9%). Among PT patients with DM, the most frequently prescribed index drug class was combination therapy (JMDC: 46.7%; MDV: 53.6%), followed by a moderate statin (JMDC: 20.0%, MDV: 14.7%), and then a fibrate in the JMDC database (10.7%), or a SICTI (7.7%) in the MDV database (Fig. 1B). Combinations prescribed as the index prescription in PT patients most commonly comprised a moderate statin plus a PUFA (JMDC: 14.3%, MDV: 17.5%), SICTI (JMDC: 10.1%, MDV: 11.6%), or fibrate (JMDC: 5.4%, MDV: 3.0%).

In the ASCVD sub-cohort, the most common hyperlipidemia drug class prescribed as first-line therapy in UT patients was a moderate statin (JMDC: 75.4%, MDV: 78.5%), followed by a PUFA (JMDC: 11.0%, MDV: 8.6%), and a fibrate (JMDC: 6.6%, MDV: 3.7%) (Fig. 2A). The most frequent index drug class among ASCVD PT patients was combination therapy (JMDC: 49.3%; MDV: 53.3%), followed by a moderate statin (JMDC: 16.4%, MDV: 15.0%), and a PUFA (JMDC: 10.1%, MDV: 8.8%) (Fig. 2B). The most common combinations prescribed in PT patients were a moderate statin plus a PUFA (JMDC: 20.9%, MDV: 20.6%), SICTI (JMDC: 9.1%, MDV: 10.0%), or fibrate (JMDC: 2.9%, MDV: 2.2%).

3.3. Persistence

Kaplan–Meier analysis of time to discontinuation of treatment by hyperlipidemia index drug class during the 12-month follow-up period in the DM (Table 2, Supplementary Fig. 3) and ASCVD (Table 2, Supplementary Fig. 4) sub-cohorts revealed a generally lower probability of continuing treatment among patients in the JMDC database compared with the MDV database.

Among UT patients in the DM sub-cohort, the continuation (persistence) rates at 12 months across all hyperlipidemia drugs as monotherapy were 60.5% (JMDC) and 64.2% (MDV). The persistence rates across all drugs including combinations were 60.2% (JMDC) and 63.8% (MDV). The persistence rate was highest with a moderate statin in both the JMDC (63.7%) and MDV (65.7%) databases (Table 2). The persistence rate was lowest with an intensive statin in the MDV database (28.8%); a comparable rate was observed in the JMDC database (28.9%). Among PT patients in the DM sub-cohort, the persistence rates at 12 months across all drugs as monotherapy only and combinations in the two databases were as follows: monotherapy only, 59.5% (JMDC) and 64.2% (MDV); and combinations, 60.7% (JMDC) and 66.1% (MDV). Persistence rates ranged from 51.8% to 72.2% for all categories except for ‘other’ hyperlipidemia drugs, where the rates were noticeably lower, both in the JMDC (27.8%) and the MDV (25.9%) databases.

In the ASCVD sub-cohort, the 12-month persistence rate in UT patients across all hyperlipidemia drugs as monotherapy were 60.8% (JMDC) and 59.4% (MDV). The persistence rates across all drugs including combinations were 60.4% (JMDC) and 59.1% (MDV). The persistence rate was highest with a moderate statin in both the JMDC (63.8%) and MDV (61.4%) databases (Table 2). Persistence rates with intensive statins were low in both the JMDC (42.9%) and MDV (39.1%) databases, with the lowest persistence rates of 35.7% (JMDC) and 31.2% (MDV) observed with ‘other’ hyperlipidemia drugs. Among PT patients, the persistence rates at 12 months across all drugs in JMDC and MDV were 56.3% and 61.5%, respectively, for monotherapy only, and 60.5% and 65.1%, respectively, for combinations. Persistence rates for a moderate statin was relatively high compared with other drug classes in both the JMDC (71.4%) and MDV (70.1%) databases. Persistence rates at 12 months varied from 46.9% to 71.5% in all categories except for ‘other’ hyperlipidemia drug, where the lowest rates were observed for both JMDC (16.7%) and MDV (22.4%) databases.

Table 1
Baseline demographic and clinical characteristics in the diabetes mellitus and ASCVD sub-cohorts.

Characteristics	Diabetes mellitus						ASCVD					
	JMDC			MDV			JMDC			MDV		
	UT	PT	All patients	UT	PT	All patients	UT	PT	All patients	UT	PT	All patients
	n = 8883 (75.8%)	n = 2835 (24.2%)	n = 11,718 (100%)	n = 18,422 (81.0%)	n = 9324 (41.0%)	n = 27,746 (100%)	n = 2948 (71.9%)	n = 1153 (28.1%)	n = 4101 (100%)	n = 9201 (64.1%)	n = 5155 (35.9%)	n = 14,356 (100%)
Follow-up duration (days), mean ± SD	713 ± 204	727 ± 205	717 ± 204	783 ± 216	809 ± 218	792 ± 217	702 ± 202	733 ± 209	711 ± 205	781 ± 220	807 ± 218	791 ± 220
Age at index date (years), mean ± SD	52.6 ± 9.3	55.1 ± 8.8	53.2 ± 9.2	67.3 ± 12.0	66.1 ± 11.5	66.9 ± 11.9	55.6 ± 8.9	57.0 ± 8.8	56.0 ± 8.9	71.7 ± 10.3	69.2 ± 10.6	70.8 ± 10.5
Male gender, n (%)	6213 (69.9)	2068 (72.9)	8281 (70.7)	10,740 (58.3)	5570 (59.7)	16,310 (58.8)	1916 (65.0)	801 (69.5)	2717 (66.3)	5695 (61.9)	3217 (62.4)	8912 (62.1)
Multiple medications,[a] mean ± SD	2.4 ± 3.3	3.4 ± 3.4	2.6 ± 3.3	3.2 ± 2.1	3.8 ± 2.0	3.4 ± 2.1	2.1 ± 3.1	3.3 ± 3.6	2.5 ± 3.3	3.7 ± 2.1	4.1 ± 2.1	3.9 ± 2.1
Charlson Comorbidity Index,[b] mean ± SD	1.3 ± 1.6	1.7 ± 1.8	1.4 ± 1.6	2.9 ± 2.4	2.8 ± 2.2	2.9 ± 2.3	1.7 ± 1.6	2.2 ± 1.8	1.9 ± 1.7	3.2 ± 2.2	3.2 ± 2.1	3.2 ± 2.2
Comorbidity at baseline, n (%)												
Type 2 diabetes mellitus	8404 (94.6)	2800 (98.8)	11,204 (95.6)	18,108 (98.3)	9252 (99.2)	27,360 (98.6)	1008 (34.2)	577 (50.0)	1585 (38.6)	5073 (55.1)	3467 (67.3)	8540 (59.5)
Hypertension	4370 (49.2)	1886 (66.5)	6256 (53.4)	12,972 (70.4)	7345 (78.8)	20,317 (73.2)	1715 (58.2)	813 (70.5)	2528 (61.6)	7283 (79.2)	4341 (84.2)	11,624 (81.0)
Chronic kidney disease	251 (2.8)	150 (5.3)	401 (3.4)	1475 (8.0)	748 (8.0)	2223 (8.0)	118 (4.0)	73 (6.3)	191 (4.7)	825 (9.0)	436 (8.5)	1261 (8.8)
Stroke	371 (4.2)	167 (5.9)	538 (4.6)	2423 (13.2)	1425 (15.3)	3848 (13.9)	915 (31.0)	276 (23.9)	1191 (29.0)	4589 (49.9)	2127 (41.3)	6716 (46.8)
Peripheral artery disease	548 (6.2)	315 (11.1)	863 (7.4)	2459 (13.3)	2067 (22.2)	4526 (16.3)	1282 (43.5)	596 (51.7)	1878 (45.8)	3779 (41.1)	2842 (55.1)	6621 (46.1)
Coronary heart disease	249 (2.8)	112 (4.0)	361 (3.1)	718 (3.9)	488 (5.2)	1206 (4.3)	405 (13.7)	170 (14.7)	575 (14.0)	1330 (14.5)	719 (13.9)	2049 (14.3)

ASCVD, atherosclerotic cardiovascular diseases; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; SD, standard deviation; UT, untreated.

[a] Number of ATC3 codes at index date.

[b] Number of comorbidities within 3 months before the index date.

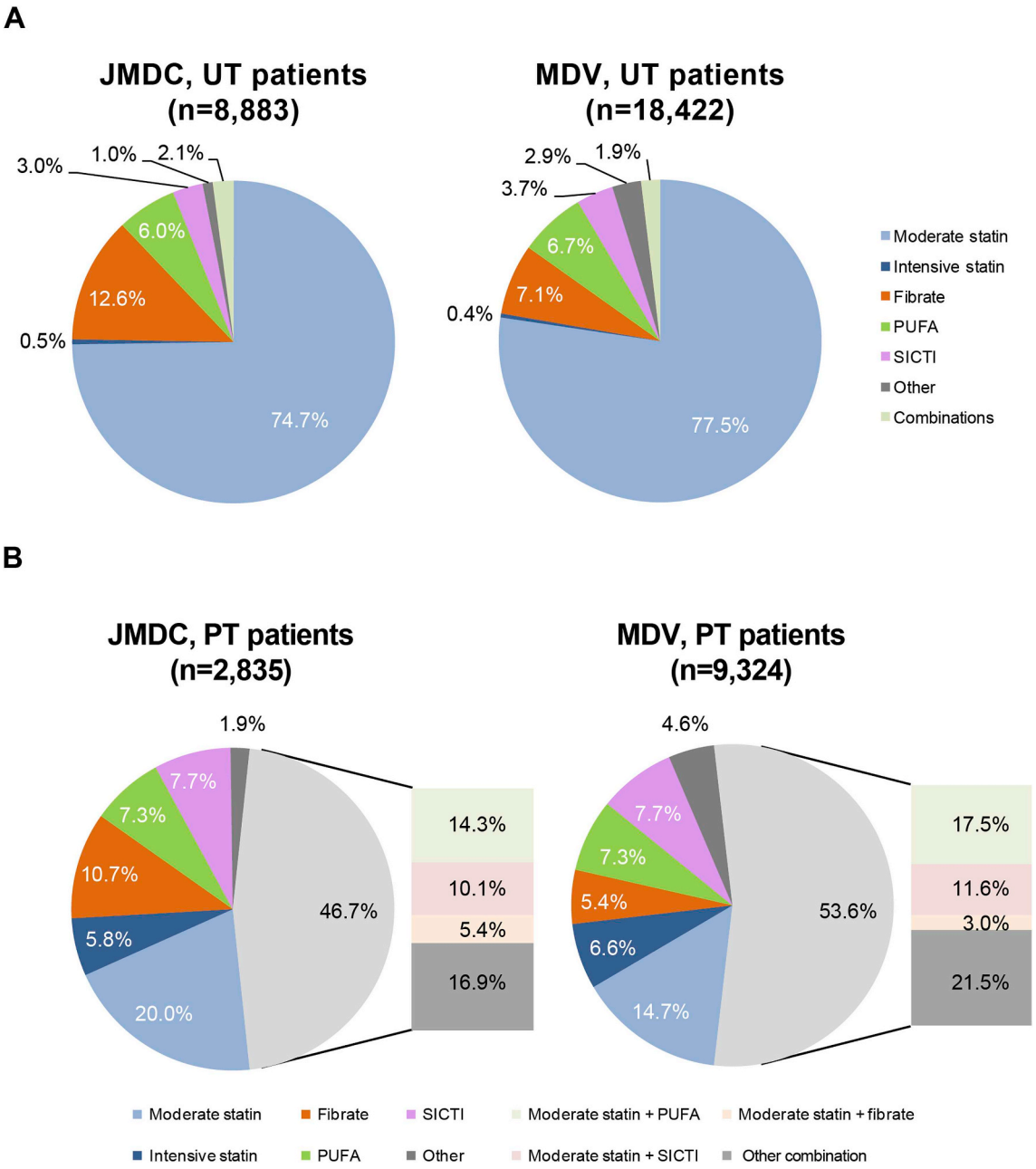

Fig. 1. Distribution of index hyperlipidemia drug classes among (A) untreated and (B) previously treated patients in the diabetes mellitus sub-cohort of the JMDC and MDV databases.
Intensive statin = atorvastatin ≥20 mg, rosuvastatin ≥10 mg, pitavastatin ≥4 mg; Moderate statin = pravastatin, simvastatin, fulvastatin, atorvastatin < 20 mg, rosuvastatin < 10 mg, pitabastatin < 4 mg; Other = anion exchange resins and nicotinic acid derivatives; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; PUFA, polyunsaturated fatty acid; SICTI, small intestine cholesterol transporter inhibitors; UT, untreated.

3.4. Adherence

Adherence to treatment within different hyperlipidemia drug classes of interest, expressed as PDC in first-line use with a single index drug class, is shown in Table 3 for both DM and ASCVD sub-cohorts. In the DM sub-cohort, for both UT and PT patients in either database (JMDC or MDV), adherence (PDC ≥0.80) rates were ≥80% across the hyperlipidemia index drug classes, except for an adherence rate of 74.6% to 'other' hyperlipidemia drugs in UT patients in the JMDC database. In the ASCVD sub-cohort, adherence rates were ≥80% across hyperlipidemia drug classes for UT and PT patients in both databases, except for a rate of 77.9% with fibrate medications in PT patients in the JDMC database.

In both sub-cohorts, adherence rates across index drug classes in UT or PT patients were generally lower in the JMDC database (DM: 74.6–89.7%; ASCVD: 77.9–97.0%) than the MDV database (DM: 86.6–97.0%; ASCVD: 92.8–97.6%). Adherence rates across index drug classes were broadly comparable between UT and PT patients within each database in both the DM (JMDC: 74.6–89.7% [UT] *vs.* 82.5–89.7% [PT]; MDV: 86.6–96.4% [UT] *vs.* 94.8–97.0% [PT]) and ASCVD (JMDC: 85.0–94.4% [UT] *vs.* 77.9–97.0% [PT]; MDV: 93.1–96.5% [UT] *vs.* 92.8–97.6% [PT]) sub-cohorts.

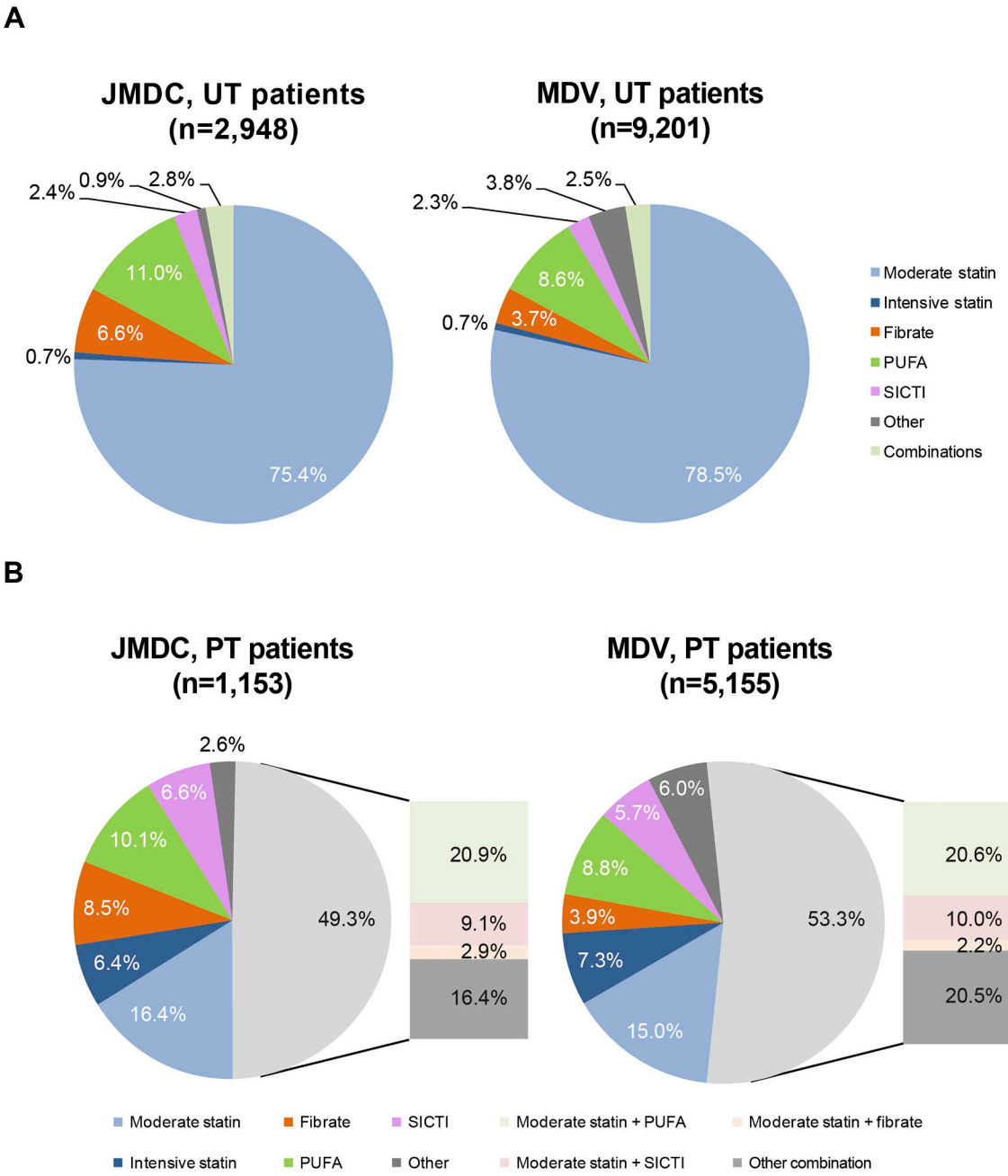

Fig. 2. Distribution of index hyperlipidemia drug classes among (A) untreated and (B) previously treated patients in the ASCVD sub-cohort of the JMDC and MDV databases.
Intensive statin = atorvastatin ≥20 mg, rosuvastatin ≥10 mg, pitavastatin ≥4 mg; Moderate statin = pravastatin, simvastatin, fulvastatin, atorvastatin < 20 mg, rosuvastatin < 10 mg, pitabastatin < 4 mg; Other = anion exchange resins and nicotinic acid derivatives; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; PUFA, polyunsaturated fatty acid; SICTI, small intestine cholesterol transporter inhibitors; UT, untreated.

4. Discussion

This sub-analysis of a retrospective, longitudinal, observational cohort study assessed treatment patterns of, persistence with, and adherence to therapies within hyperlipidemia drug classes in sub-cohorts of patients with DM and ASCVD using medical claims information from the JMDC and MDV administrative claims databases in Japan. The analysis evaluated whether Japanese patients at increased risk of CVD are treated differently to the general hyperlipidemia patient population, and explored how well these patients adhere to and persist with their prescribed treatment(s).

Despite all patients in both sub-cohorts having additional cardiovascular risk factors, the overall findings were remarkably similar to those reported for the main hyperlipidemia patient population [18]. Differences between the two database populations in both sub-cohorts were consistent with those reported previously [18], and were reflective of the two distinct insured populations (**Supplementary Methods**). Likewise, analysis of hyperlipidemia drug classes used as index therapy in the DM and ASCVD sub-cohorts revealed a similar profile to the main study population [18]. Approximately three quarters of UT patients in the DM and ASCVD sub-cohorts were prescribed a single moderate statin as first-line index treatment, likely reflecting the fact that most clinical data in at-risk patients relates to moderate statins [9,19–26]. Statins are also recommended by JAS as the first hyperlipidemia drug of choice [2,8,9]. In PT patients, approximately half were prescribed combinations as their index therapy—usually a two-drug

Table 2
Persistence to index hyperlipidemia drug classes in the DM and ASCVD sub-cohorts.

		Moderate statin	Intensive statin	Fibrate	PUFA	SICTI	Other
Persistence for DM cohort							
JMDC							
UT patients							
N		6640	45	1115	536	270	91
Time to discontinuation (days)	Mean (SE)	657 (5.6)	191 (31.2)	509 (12.3)	474 (16.2)	455 (22.1)	245 (32.0)
	Median	837	60	407	392	366	99
Continuation at 12 months, %		63.7	28.9	52.5	51.7	50.4	25.3
PT patients							
N		566	164	303	207	217	54
Time to discontinuation (days)	Mean (SE)	684 (18.4)	440 (25.9)	506 (20.3)	574 (32.0)	537 (26.0)	284 (45.3)
	Median	1056	402	448	520	556	144
Continuation at 12 months, %		67.7	51.8	55.1	57.5	59.9	27.8
MDV							
UT patients							
N		14,268	80	1307	1227	676	527
Time to discontinuation (days)	Mean (SE)	524 (3)	265 (38.4)	519 (9.9)	494 (10.1)	529 (13.7)	302 (13.7)
	Median	562	57	556	512	566	151
Continuation at 12 months, %		65.7	28.8	64.5	59.4	65.1	36.4
PT patients							
N		1366	620	504	685	718	433
Time to discontinuation (days)	Mean (SE)	585 (9.5)	539 (13.3)	522 (15.5)	525 (13.4)	545 (12.9)	233 (14.9)
	Median	616	567	560	560	560	70
Continuation at 12 months, %		72.2	71.3	63.3	62.8	68.0	25.9
Persistence for ASCVD cohort							
JMDC							
UT patients							
N		2224	21	196	323	72	28
Time to discontinuation (days)	Mean (SE)	647 (9.4)	449 (95.9)	502 (29.2)	484 (23.5)	474 (41.8)	274 (54.4)
	Median	936	281	393	367	473	124
Continuation at 12 months, %		63.8	42.9	52.6	50.2	55.6	35.7
PT patients							
N		189	74	98	117	76	30
Time to discontinuation (days)	Mean (SE)	655 (27.7)	509 (42.5)	457 (37.3)	493 (39.0)	490 (39.2)	196 (57.3)
	Median	NE	840	337	354	563	54
Continuation at 12 months, %		71.4	58.1	46.9	48.7	56.6	16.7
MDV							
UT patients							
N		7219	69	336	787	210	353
Time to discontinuation (days)	Mean (SE)	493 (4.3)	314.0 (41.5)	494 (20.7)	464.0 (13.1)	510 (26)	274 (17.2)
	Median	537	80	531	464	546	98
Continuation at 12 months, %		61.4	39.1	60.4	54.4	61.4	31.2
PT patients							
N		772	376	201	456	293	308
Time to discontinuation (days)	Mean (SE)	559 (12.9)	548 (17.3)	478 (25.2)	519 (17.3)	568 (20.1)	222 (17.9)
	Median	595	574	504	560	581	59
Continuation at 12 months, %		70.1	71.5	58.2	60.5	71.0	22.4

Intensive statin = atorvastatin ≥20 mg, rosuvastatin ≥10 mg, pitavastatin ≥4 mg; Moderate statin = pravastatin, simvastatin, fulvastatin, atorvastatin < 20 mg, rosuvastatin < 10 mg, pitabastatin < 4 mg; Other = anion exchange resins and nicotinic acid derivatives. ASCVD, atherosclerotic cardiovascular diseases; DM, diabetes mellitus; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PT, previously treated; PUFA, polyunsaturated fatty acid; SE, standard error; SICTI, small intestine cholesterol transporter inhibitors; UT, untreated.

regimen including a moderate statin—with 15–20% receiving a single moderate statin. Initial use of an intensive statin was low in both UT (< 1%) and PT (6–7%) patients, reflecting another recently reported analysis using data from the JMDC database [27]. The low use of intensive statins in UT and PT patients and of combination regimens in UT patients was surprising given the strict lipid management targets for Japanese patients with DM and with a history of CVD/cerebrovascular disease [2,9], and suggests that these patients may be being undertreated. However, data on the effect of treatment on lipid levels would be required to confirm this. Three large observational studies have indicated that JAS lipid targets are not being met in a substantial proportion of Japanese patients with hyperlipidemia, with up to one-third of treated patients in routine care settings failing to achieve their LDL-C goals, and 45–66% of patients with a history of CHD not reaching their LDL-C target of < 100 mg/dL [13,14,16]. It was recently reported that 69% and 90% of patients with diagnosed or suspected familial hypercholesterolemia, respectively, remained on statin monotherapy despite failing to achieve their LDL-C target of < 100 mg/dL [28]. Another recent study found only 30–58% of patients with high cardiovascular risk achieved LDL-C target of < 100 mg/dL [29]. According to 2012 and 2017 JAS guidelines, achievement of strict lipid management targets often necessitates use of higher doses and/or combinations of agents from several hyperlipidemia drug classes [2,8,9].

Adherence to hyperlipidemia medications was generally high. This finding is consistent with the results of a meta-analysis of 22 cohort studies, which reported favorable adherence to statins in patients with a history of CVD, and in those with comorbid hypertension or DM [30]. Another study has shown that hyperlipidemia patients with pre-existing comorbidities tend to adhere better to LLTs than those without concomitant conditions [31], potentially due to a greater awareness of the importance of adherence for reducing cardiovascular risk [32].

In contrast to adherence rates, 12-month persistence rates were low and variable across drug classes and databases, which is concerning given the association between poor persistence with hyperlipidemia medications and CVD risk [11]. Notably, patients who discontinue treatment may not benefit from the time-dependent increase in

Table 3
Adherence to index hyperlipidemia drug classes in the diabetes mellitus and ASCVD sub-cohorts.

	Moderate statin	Intensive statin	Fibrate	PUFA	SICTI	Other
Adherence for DM cohort						
JMDC						
UT patients						
N	5920	32	947	455	223	67
PDC, mean ± SD	0.91 ± 0.10	0.93 ± 0.14	0.91 ± 0.10	0.92 ± 0.10	0.92 ± 0.10	0.87 ± 0.13
Adherent,[a] n (%)	5213 (88.1)	28 (87.5)	817 (86.3)	397 (87.3)	200 (89.7)	50 (74.6)
PT patients						
N	520	136	284	175	195	40
PDC, mean ± SD	0.92 ± 0.09	0.92 ± 0.09	0.91 ± 0.10	0.92 ± 0.10	0.91 ± 0.10	0.91 ± 0.11
Adherent,[a] n (%)	463 (89.0)	121 (89.0)	249 (87.7)	157 (89.7)	173 (88.7)	33 (82.5)
MDV						
UT patients						
N	13,096	67	1162	1086	610	402
PDC, mean ± SD	0.96 ± 0.08	0.94 ± 0.13	0.96 ± 0.08	0.96 ± 0.07	0.96 ± 0.10	0.95 ± 0.10
Adherent,[a] n (%)	12,549 (95.8)	58 (86.6)	1111 (95.6)	1047 (96.4)	586 (96.1)	375 (93.3)
PT patients						
N	1256	528	436	616	629	310
PDC, mean ± SD	0.97 ± 0.07	0.96 ± 0.07	0.96 ± 0.08	0.97 ± 0.06	0.96 ± 0.09	0.96 ± 0.10
Adherent,[a] n (%)	1218 (97.0)	512 (97.0)	419 (96.1)	597 (96.9)	599 (95.2)	294 (94.8)
Adherence for ASCVD cohort						
JMDC						
UT patients						
N	2006	16	166	266	59	18
PDC, mean ± SD	0.92 ± 0.10	0.95 ± 0.07	0.91 ± 0.09	0.91 ± 0.10	0.92 ± 0.10	0.92 ± 0.07
Adherent,[a] n (%)	1795 (89.5)	15 (93.8)	150 (90.4)	226 (85.0)	53 (89.8)	17 (94.4)
PT patients						
N	174	61	86	99	67	21
PDC, mean ± SD	0.94 ± 0.07	0.95 ± 0.07	0.89 ± 0.11	0.92 ± 0.08	0.94 ± 0.05	0.91 ± 0.15
Adherent,[a] n (%)	166 (95.4)	59 (96.7)	67 (77.9)	90 (90.9)	65 (97.0)	17 (81.0)
MDV						
UT patients						
N	6619	58	296	684	190	258
PDC, mean ± SD	0.97 ± 0.08	0.96 ± 0.12	0.96 ± 0.08	0.97 ± 0.06	0.96 ± 0.11	0.96 ± 0.09
Adherent,[a] n (%)	6378 (96.4)	54 (93.1)	284 (96.0)	660 (96.5)	181 (95.3)	245 (95.0)
PT patients						
N	701	324	168	401	267	208
PDC, mean ± SD	0.97 ± 0.06	0.97 ± 0.07	0.96 ± 0.11	0.97 ± 0.07	0.97 ± 0.08	0.95 ± 0.12
Adherent,[a] n (%)	684 (97.6)	315 (97.2)	160 (95.2)	391 (97.5)	259 (97.0)	193 (92.8)

Intensive statin = atorvastatin ≥20 mg, rosuvastatin ≥10 mg, pitavastatin ≥4 mg; Moderate statin = pravastatin, simvastatin, fluvastatin, atorvastatin < 20 mg, rosuvastatin < 10 mg, pitavastatin < 4 mg; Other = anion exchange resins and nicotinic acid derivatives. ASCVD, atherosclerotic cardiovascular diseases; DM, diabetes mellitus; JMDC, Japan Medical Data Center; MDV, Medical Data Vision; PDC, proportion of days covered (medical possession ratio); PT, previously treated; PUFA, polyunsaturated fatty acid; SD, standard deviation; SICTI, small intestine cholesterol transporter inhibitors; UT, untreated.

[a] PDC ≥0.80.

treatment benefits of LLTs, as observed in several large-scale studies including LIPID [33] and WOSCOPS [34]. Regardless of treatment history, persistence rates were among the highest in patients prescribed moderate statins [9] and among the lowest in patients prescribed intensive statins. Across both sub-cohorts, persistence rates were generally lower in UT versus PT patients, possibly reflecting differences in the relative value these sub-groups place on treatment. Lower persistence rates observed with intensive statins in UT patients compared with PT patients may have resulted from a lower tolerance for any side effects in UT patients than in PT patients for any side effects associated with high-dose statin therapy. Poor tolerability is the most common reason for discontinuing hyperlipidemia medication [33,34]. In addition, other reasons such as a nocebo effect or down-titration as part of a treatment regimen could have contributed to the high withdrawal rate. Factors related to continuation of statin therapy are complex [35], and were not addressed in this study.

In our study, persistence rates were low and variable despite consistently high adherence rates, suggesting that patients may not be adequately medicated even with high adherence rates. Of note, adherence rates derived from claims data may be overestimated in Japan, as patients rarely request changes to their prescription before completing the previous course of medication [36]. The low and variable persistence rates (16.7–72.2%) observed in our study are in contrast to those previously reported by Nagar et al. (60.0–63.4%) [27]. Patients without hyperlipidemia were included in their study (31.6–35.2%), while our study included only patients diagnosed with hyperlipidemia, who were therefore expected to have greater awareness of their condition; however, this was not reflected in the persistence rates.

The strengths and limitations of this analysis have been discussed previously [18]. In brief, this analysis provides valuable information on many hyperlipidemia patients with continuous enrollment included in two large administrative claims databases. However, the study is limited by its observational nature, strict eligibility criteria, limited follow-up (12 months), small sample sizes in some sub-groups, and a lack of statistical power to detect differences between sub-groups of interest. There was also an assumption that all patients filled their prescriptions and took their medication. Additionally, baseline lipid levels and subsequent treatment-related changes, which would have influenced treatment decision-making, were not captured systematically. Further information missing from both databases included reasons for discontinuing treatment, whether patients took extra doses to compensate for forgotten doses, incidence of pill dumping or stockpiling, details of non-reimbursed treatments, and data on the impact of treatment on symptoms/health outcomes. Specific limitations associated with the JMDC database included a lack of information on elderly patients (as beneficiaries were working adults and their family members) and non-validated diagnoses. For the MDV database, there is no linkage of data between medical care facilities. Therefore, if a patient receives care in

different institutions, their data will be incomplete.

In summary, the results of this retrospective, observational, cohort sub-study indicate that many Japanese patients with hyperlipidemia and DM or ASCVD are prescribed single-agent LLT, most commonly a moderate statin, as their index drug, and therefore may not be receiving adequate treatment to reach their strict lipid management goals. While adherence rates with hyperlipidemia drugs were generally high, persistence rates were low, which is concerning given the link between poor persistence and CVD, particularly in these at-risk patient populations. Studies are needed to determine the reasons behind the limited prescribing of more aggressive therapies (intensive statins and combinations) and low persistence rates, and to identify ways of supporting these patients with DM or ASCVD to remain on therapy and lower their cardiovascular risk profile.

Conflicts of interest

Mayumi Wake, Akinori Oh, and Yukio Shimasaki are current employees of Takeda Pharmaceutical Company Limited.

Yoshie Onishi and Florent Guelfucci are current employees of Creativ-Ceutical.

Tamio Teramoto has received: remuneration (e.g. lecture fees) from Bayer Yakuhin Ltd, Pfizer Japan Inc., Sanofi K.K., Amgen Astellas BioPharm; scholarship funds or donations from Daiichi-Sankyo Co Ltd. and KISSEI Pharmaceutical Co Ltd. Tamio Teramoto is affiliated with an endowed department sponsored by Bayer Yakuhin Ltd., MSD K.K., MOCHIDA Pharmaceutical Co Ltd., and Kowa Company Ltd.

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Author contributions

MW, YO, FG, YS and TT are responsible for the work described in this paper.

MW, YO, FG, YS and TT were involved in the conception, design, or planning of the study.

YO and FG were involved in the analysis of data.

MW, YO, AO, and TT were involved in the interpretation of results.

MW, AO, YO, FG and TT substantially contributed to the drafting of the manuscript.

The manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2018.12.026.

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